One aspect as reported herein is a disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains,
- one antibody Fc-region, and
- one or more antigen binding sites,

wherein the antigen presenting domain comprises in N- to C-terminal direction

either

(i) a β2-microglobulin, and

(ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %,

or

(i) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %, and

(ii) a β2-microglobulin,

or

(i) a T-cell response eliciting peptide,

(ii) a β2-microglobulin, and

(iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more,

or

(i) a T-cell response eliciting peptide,

(ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more, and

(iii) a β2-microglobulin,

wherein the antigen binding site binds to a cancer cell surface antigen,

wherein the antigen presenting domain comprises ~~has at least two non-naturally occurring cysteine residues that form~~ an intrachain/interdomain disulfide bond which is formed between a first cysteine residue that is arranged in the linker connecting the T-cell response eliciting peptide and β2-microglobulin and a second cysteine residue that is introduced in the extracellular domains α1, α2, and α3 of the class I MHC molecule.

In one embodiment one non-naturally occurring cysteine residue in the antigen presenting domain is in the linker between T-cell response eliciting peptide and one

~~Amended~~ Patent Claims

1. A disulfide-linked multivalent multi-function protein, characterized in that it comprises

- one or two antigen presenting domains,

- one antibody Fc-region, and

- one or more antigen binding sites,

wherein the antigen presenting domain comprises in N- to C-terminal direction

either

(i) a β2-microglobulin, and

(ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %,

or

(i) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of less than 1 %, and

(ii) a β2-microglobulin,

or

(i) a T-cell response eliciting peptide,

(ii) a β2-microglobulin, and

(iii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more,

or

(i) a T-cell response eliciting peptide,

(ii) the extracellular domains α1, α2, and α3 of a class I MHC molecule with a relative frequency of 1 % or more, and

(iii) a β2-microglobulin,

wherein the antigen binding site binds to a cancer cell surface antigen,

wherein the antigen presenting domain comprises ~~has at least two non-naturally occurring cysteine residues that form~~ an intrachain/interdomain disulfide bond which is formed between a first cysteine residue that is arranged in the linker connecting the T-cell response eliciting peptide and β2-microglobulin and a second cysteine residue that is introduced in the extracellular domains α1, α2, and α3 of the class I MHC molecule.

~~2. The disulfide-linked multivalent multi-function protein according to claim 1, characterized in that one non-naturally occurring cysteine residue in the antigen presenting domain is in the linker between T-cell response eliciting peptide and one non-naturally occurring cysteine residue is in one of the extracellular domains α1, α2, and α3 of the class I MHC molecule.~~

~~3. The disulfide-linked multivalent multi-function protein according to any one of claims 1 or 2, characterized in that~~

~~the antigen presenting domain has cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond, or~~

~~the antigen presenting domain has cysteine residues at least at position 11 and at position 108 and the cysteine residues at position 11 and position 108 form a disulfide bond.~~

4~~2~~. The disulfide-linked multivalent multi-function protein according to ~~any one of~~ claim~~s~~ 1 ~~to 3~~, characterized in that the antibody Fc-region comprises a first Fc-region polypeptide and a second Fc-region polypeptide, which are disulfide linked with each other, whereby the antigen binding site or one of the antigen binding sites comprises the first Fc-region polypeptide and the second antigen binding site, if present, comprises the second Fc-region polypeptide.

5~~3~~. The disulfide-linked multivalent multi-function protein according to ~~any one of~~ claim~~s~~ 1 ~~to 4~~or 2, characterized in that the antigen binding site comprises i) a pair of an antibody heavy chain and an antibody light chain, or ii) a scFv fusion polypeptide comprising in N- to C-terminal direction a scFv antibody fragment and an antibody Fc-region polypeptide, or iii) a scFab fusion polypeptide comprising in N- to C-terminal direction a scFab and an antibody Fc-region polypeptide,

or

the antigen binding sites comprise independently of each other i) a (cognate) pair of an antibody heavy chain and an antibody light chain, whereby the individual chains can be wild-type chains or modified chains (substituted, mutated or domain exchanged), or ii) a scFv fusion polypeptide comprising in N- to C-terminal direction a scFv antibody fragment and an antibody Fc-region polypeptide, or iii) a scFab fusion polypeptide comprising in N- to C-terminal direction a scFab and an antibody Fc-region polypeptide.

~~6~~4. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to ~~5~~3, characterized in that i) an antigen presenting domain is linked to the N-terminus of the heavy chain or to the N-terminus of the light chain of an antigen binding site, or ii) one antigen presenting domain is linked to each N-terminus of the heavy chain or to each N-terminus of the light chain of each antigen binding site, or iii) an antigen presenting domain is linked to the C-terminus of the heavy chain or to the C-terminus of the light chain of the antigen binding site, or vi) one antigen presenting domain is linked to each C-terminus of the heavy chain or to each C-terminus of the light chain of each antigen binding site, or v) an antigen presenting domain is linked to the N- or C-terminus of an scFv fusion polypeptide, or vi) one antigen presenting domain is linked to each N- or C-terminus of each scFv fusion polypeptide, or vii) an antigen presenting domain is linked to the N- or C-terminus of a scFab fusion polypeptide, or viii) one antigen presenting domain is linked to each N- or C-terminus of each scFab fusion polypeptide, or ix) an antigen presenting domain is linked to the N- or C-terminus of the second Fc-region polypeptide, or x) one antigen presenting domain is linked to the N- or C-terminus of the first Fc-region polypeptide and one antigen presenting domain is linked to the N- or C-terminus of the second Fc-region polypeptide.

~~7~~5. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to ~~6~~4, characterized in that the T-cell response eliciting peptide is a human cytomegalovirus-derived peptide.

~~8~~6. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to ~~7~~5, characterized in that the virus-derived peptide has the amino acid sequence of SEQ ID NO: 01.

~~97~~. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to ~~86~~, characterized in that the class I MHC molecule with a relative frequency of 1 % or more is selected from the group comprising HLA-A*0201, HLA-A*1101, HLA-A*2402, HLA-A*340101, HLA-C*0304, HLA-C*0401, and HLA-C*0702.

~~108~~. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to 9, characterized in that the class I MHC molecule with a relative frequency of less than 1 % is selected from the group comprising HLA-B*4201, HLA-B*5901, HLA-B*6701, and HLA-B*7802.

~~11. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to 10, characterized in that the antigen presenting domain comprises~~

~~(i) a virus-derived peptide,~~
~~(ii) β2-microglobulin,~~
~~(iii) the soluble HLA-A allele A*0201, and~~
~~(iv) cysteine residues at least at position 11 and at position 227 and the cysteine residues at position 11 and position 227 form a disulfide bond.~~

~~12. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to 11, characterized in that the antigen presenting domain comprises in N- to C-terminal direction~~

~~(i) a virus-derived peptide that has an amino acid sequence selected from the group comprising SEQ ID NO: 01 to SEQ ID NO: 70,~~
~~(ii) a first linker peptide that has an amino acid sequence selected from the group comprising SEQ ID NO: 77, 78, 79, 82, 83, 84, and 139~~
~~(iii) a β2-microglobulin that has an amino acid sequence of SEQ ID NO: 71,~~
~~(iv) a second linker peptide that has an amino acid sequence selected from the group comprising SEQ ID NO: 77, 78, 79, 82, 83, and 84,~~
~~(v) the extracellular domains α1, α2, and α3 of a class I MHC molecule that has an amino acid sequence of SEQ ID NO: 140,~~
~~(vi) a third linker peptide that has an amino acid sequence selected from the group comprising SEQ ID NO: 73, 77, 78, 79, 82, 83, 84, and 136, and~~

~~(vii) cysteine residues at least at position 11 and at position 227 and a disulfide bond between the cysteine residues at position 11 and position 227.~~

~~13~~9. A pharmaceutical formulation comprising the disulfide-linked multivalent multi-function protein according to any one of claims 1 to ~~12~~ 8 and optionally a pharmaceutically acceptable carrier.

~~14~~10. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to ~~12~~ 8 for use as a medicament.

~~15~~11. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to ~~12~~ 8 for use in treating cancer.

~~16~~12. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to ~~12~~ 8 for use in attracting virus-specific cytotoxic T-cells of an individual to a target.

~~17~~13. The disulfide-linked multivalent multi-function protein according to any one of claims 1 to ~~12~~ 8 for use in removal of cancer cells or virus infected cells.